The role of statins- New Approaches

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Cholesterol Trialist Collaboration
Meta-Analysis of Dyslipidemia Trials

Major Vascular Events

Proportional Reduction in Event Rate (SE)

Reduction in LDL Cholesterol (mmol/L)

Adapted from CTT Collaborators. *Lancet.* 2005; 366:1267-78
Greater absolute benefit in secondary vs primary prevention with more intensive Tx

Mean LDL-C level at follow-up (mmol/L)

% with CHD event

ATP III  JBS2 /ESC  GMS

2° Prevention

1° Prevention
## Meta-Analysis of Intensive Statin Therapy

### LDL Cholesterol by Trial

<table>
<thead>
<tr>
<th></th>
<th>ACS</th>
<th>Stable CAD</th>
<th>Pooled</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>n</strong></td>
<td>4162</td>
<td>10001</td>
<td>27548</td>
</tr>
<tr>
<td><strong>Prior Statin Use</strong></td>
<td>25.2%</td>
<td>0%</td>
<td>75.5%</td>
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### Patients

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### LDL-C (mg/dL)

<table>
<thead>
<tr>
<th></th>
<th>PROVE IT-TIMI 22</th>
<th>A-to-Z</th>
<th>TNT</th>
<th>IDEAL</th>
<th>Pooled</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td>108.4</td>
<td>112.9</td>
<td>152</td>
<td>121.5</td>
<td>129.6</td>
</tr>
<tr>
<td><strong>Standard</strong></td>
<td>97.1</td>
<td>101</td>
<td>101</td>
<td>104</td>
<td>101.4</td>
</tr>
<tr>
<td><strong>Intensive</strong></td>
<td>65.5</td>
<td>69.1</td>
<td>77</td>
<td>81</td>
<td>75.4</td>
</tr>
</tbody>
</table>

# Meta-Analysis of Intensive Statin Therapy

## All Endpoints

<table>
<thead>
<tr>
<th>Event</th>
<th>Odds Ratio (95% CI)</th>
<th>Odds Reduction</th>
<th>Event Rates No./Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>High Dose</td>
</tr>
<tr>
<td>Coronary Death or Any Cardiovascular Event</td>
<td>OR, 0.84 95% CI, 0.80-0.89 <em>P</em>=.0000000000006</td>
<td>-16%</td>
<td>3972/13798 (28.8)</td>
</tr>
<tr>
<td>Coronary Death or MI</td>
<td>OR, 0.84 95% CI, 0.77-0.91 <em>p</em>=0.00003</td>
<td>-16%</td>
<td>1097/13798 (8.0)</td>
</tr>
<tr>
<td>Cardiovascular Death</td>
<td>OR, 0.88 95% CI, 0.78-1.00 <em>p</em>=.054</td>
<td>-12%</td>
<td>462/13798 (3.3)</td>
</tr>
<tr>
<td>Non-Cardiovascular Death</td>
<td>OR, 1.03 95% CI, 0.88-1.20 <em>p</em>=.73</td>
<td>+3%</td>
<td>340/13798 (2.5)</td>
</tr>
<tr>
<td>Total Mortality</td>
<td>OR, 0.94 95% CI, 0.85-1.04 <em>p</em>=.20</td>
<td>-6%</td>
<td>808/13798 (5.9)</td>
</tr>
<tr>
<td>Stroke</td>
<td>OR 0.82 95% CI, 0.71-0.96 <em>p</em>=0.012</td>
<td>-18%</td>
<td>316/13798 (2.3)</td>
</tr>
</tbody>
</table>

*Cannon CP, et al JACC 2006*
In ACS intensive statin therapy and mortality

- Meta-analysis of PROVE IT and A to Z
- *Afilalo et al Heart 2007*

- About 8500 patients with avg of 2 years of FU

- 25% reduction in all cause mortality
  - (0.61-0.93)

- Absolute benefit is 1.2%
PROVE IT-TIMI 22: Relationship Between Month 4 LDL and Long-Term Risk of Death or Major CV Event

Hazard Ratio

- >2.05 – 2.56
  - Referent
  - 0.80 (0.59, 1.07)
- >1.54 – 2.05
  - 0.67 (0.50, 0.92)
- > 1.03 -1.54
- <1.03
  - 0.61 (0.40, 0.91)

*Adjusted for age, gender, DM, prior MI, baseline LDL

Wiviott SD, et al. JACC. 2005
TNT: Incidence of First Major Cardiovascular Events Across Quintiles

LaRosa JC. AJC. 2007

*P-value for trend across LDL-C
Interpretation

- Lower is better

- In stable CHD titrate statin to achieve a lower LDL-C
  - <1.8mmol/L North American guidelines
  - <2.0mmol/L in European guidelines
Can we afford to delay intensive statin Tx in ACS?

Death/ Nonfatal MI (%)

Months Of Follow-Up

Stable CAD

Stable CAD

ACS

4S CARE LIPID/ HPS/IDEAL

PROVE IT-TIMI 22/ A to Z/ IDEAL

0 2 4 6 8 10 12 14 16
0 2 4 6 8 10 12 Years

Can we afford to delay intensive statin Tx in ACS?
Rapid early reduction in Death, MI or ACS With Intensive statin Tx <1 month

% Of Patients With Death, MI, Or Rehospitalization For ACS

Days Following Randomization

A To Z Primary End Point
CV Death, MI, Readmission ACS, Or Stroke

Placebo/ Simva 20
Rate = 16.7%

Simva 40/80
Rate = 14.4%

RR = 11%
P = 0.14

MIRACL: Primary Efficacy Measure: Time To First Event*

Death (any cause), nonfatal MI, resuscitated cardiac arrest, worsening angina with new objective evidence, and urgent rehospitalization.

RR = 16%  P = .048
95% CI = 0.701-0.999
**PROVE IT-TIMI 22 And MIRACL: CRP Appears To Be Driving The Early Time To Benefit With Intensive Atorvastatin Therapy**

<table>
<thead>
<tr>
<th></th>
<th>A-to-Z</th>
<th>MIRACL</th>
<th>PROVE IT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients randomized</td>
<td>4497</td>
<td>3086</td>
<td>4162</td>
</tr>
<tr>
<td>Early* LDL achieved on treatment, mmol/l</td>
<td>1.6</td>
<td>1.85</td>
<td>1.6</td>
</tr>
<tr>
<td>Early* LDL cholesterol differential, mmol/l</td>
<td>1.6</td>
<td>1.6</td>
<td>0.85</td>
</tr>
<tr>
<td>CRP differential, %</td>
<td>17</td>
<td>34</td>
<td>38</td>
</tr>
<tr>
<td>Early event reduction, %</td>
<td>0*</td>
<td>16*</td>
<td>18†</td>
</tr>
</tbody>
</table>

* Measured 120 days after randomization.
† Measured 90 days after randomization.
Adapted from Nissen. *JAMA.* 2004;292:1365.
Interpretation

- Only intensive statin therapy produces early benefits after ACS
- The early benefit appears to be poorly related to LDL-C reduction
- Early benefits may reflect a reduction in inflammation by pleiotropic effects
Risk of heart failure and statin therapy

Scirica et al, JACC 06

<table>
<thead>
<tr>
<th>Days from Randomization</th>
<th>Pravastatin 40mg</th>
<th>Atorvastatin 80mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. at Risk</td>
<td>Prava</td>
<td>Atorva</td>
</tr>
<tr>
<td>30</td>
<td>2063</td>
<td>2099</td>
</tr>
<tr>
<td>180</td>
<td>1930</td>
<td>1959</td>
</tr>
<tr>
<td>365</td>
<td>1846</td>
<td>1869</td>
</tr>
<tr>
<td>540</td>
<td>1785</td>
<td>1826</td>
</tr>
<tr>
<td>720</td>
<td>866</td>
<td>869</td>
</tr>
<tr>
<td>900</td>
<td>342</td>
<td>339</td>
</tr>
</tbody>
</table>

HR 0.55 (0.35, 0.85)  
P=0.008


Meta-analysis of intensive vs standard therapy for reduction of heart failure

<table>
<thead>
<tr>
<th>Study (n)</th>
<th>Treatment</th>
<th>Achieved LDL (mg/dl)</th>
<th>Odds ratio (95% CI)</th>
<th>Treatment Achieved LDL (mg/dl)</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TNT (10,001)</td>
<td>Atorvastatin 80</td>
<td>77</td>
<td>0.74 (0.58, 0.94)</td>
<td>Simvastatin 80</td>
<td>63</td>
</tr>
<tr>
<td></td>
<td>Simvastatin 80</td>
<td>63</td>
<td>0.72 (0.52, 0.98)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A to Z (4497)</td>
<td>Pravastatin 40</td>
<td>95</td>
<td>0.54 (0.34, 0.85)</td>
<td>Atorvastatin 80</td>
<td>62</td>
</tr>
<tr>
<td>PROVE IT (4162)</td>
<td>Atorvastatin 80</td>
<td>81</td>
<td>0.80 (0.61, 1.05)</td>
<td>Simvastatin 20</td>
<td>104</td>
</tr>
<tr>
<td>IDEAL (8888)</td>
<td>Atorvastatin 10</td>
<td>101</td>
<td>0.80 (0.61, 1.05)</td>
<td>Simvastatin 20</td>
<td>104</td>
</tr>
<tr>
<td>Overall (95% CI)</td>
<td></td>
<td>0.73 (0.63, 0.84), p&lt;0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
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Scirica, Morrow, Ray et al JACC 2006
Risk of heart failure according to BNP and intensity of statin therapy

HR 0.59 (0.29, 1.1) p=0.099

BNP <80 / Pravastatin (n=1482)

BNP <80 / Atorvastatin (n=215)

BNP >80 / Pravastatin (n=217)

BNP >80 / Atorvastatin (n=217)

HR 0.32 (0.13, 0.8) p=0.014

4.7% Abs risk reduction

Scirica et al, JACC 2006;47:2326-31
The Treating to New Targets (TNT) study followed 10,001 patients with stable CAD randomized to treatment with atorvastatin 80 mg or 10 mg for a median of 4.9 years. A history of HF was present in 7.8% of patients. Patients with known ejection fraction <30% and advanced HF were excluded from the study. Hospitalization for HF was a predefined secondary end point.

Conclusion

- In patients with CHD there is incremental benefit in achieving a lower LDL-C target with intensive statin therapy.
- Among patients on intensive statin therapy the lowest LDL-C levels are associated with lowest risk.
- i.e. Lower is better.

- In ACS patients intensive statin therapy initiated early after ACS is associated with early benefits.

- Early benefits are incompletely explained by LDL-C changes and may reflect pleiotropic effects.

- Intensive Tx reduces hospitalization for heart failure especially in those with prior history of heart failure or higher BNP levels.